WHO 2021 THORACIC TUMOR UPDATES

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Arizona Society of Pathologists
Fall Meeting
November 13, 2021
DISCLOSURES

• No relevant financial relationships with ineligible companies to disclose by Dr. Yasmeen M. Butt.
LEARNING OBJECTIVES

• List WHO 2021 grading criteria for pulmonary adenocarcinoma

• Describe spread through air spaces (STAS) and summarize its significance

• Formulate a differential diagnosis for high grade thoracic malignancies that includes new entities

• Be able to grade epithelioid mesotheliomas according to new criteria

• Be aware of new terminology for bronchiolar adenomas.
2021 UPDATES: NEW ENTITIES

• Overall, histopathologic classification remains intact from 4th edition

• Thoracic \textit{SMARCA4}-deficient undifferentiated tumor

• Bronchiolar adenoma/ciliated muconodular papillary tumor (new adenoma subtype)
2021 UPDATES: RE-CLASSIFIED/RE-NAMED

• Lymphoepithelioma-like carcinoma → lymphoepithelial carcinoma (EBV + and EBV -)
• Enteric adenocarcinoma → enteric-type adenocarcinoma
• Pleomorphic carcinoma (replaces giant cell and spindle cell carcinoma)
• Carcinoid tumor NOS terminology
# IASLC Histopathologic Grading Scheme for Non-Mucinous Lung Adenocarcinoma

<table>
<thead>
<tr>
<th>Grade</th>
<th>Differentiation</th>
<th>Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Well-differentiated</td>
<td>Lepidic-predominant with no or &lt;20% high-grade pattern</td>
</tr>
<tr>
<td>2</td>
<td>Moderately differentiated</td>
<td>Acinar or papillary-predominant with no or &lt;20% high-grade pattern</td>
</tr>
<tr>
<td>3</td>
<td>Poorly differentiated</td>
<td>Any tumor with ≥ 20% high-grade pattern (solid, micropapillary, cribriform, or complex glandular pattern*)</td>
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</tbody>
</table>

*S fused glands or single cells infiltrating in a desmoplastic stroma

Suggestion that a 5% cutoff may be appropriate for this grading system

TISSUE MANAGEMENT: GENERAL RECOMMENDATIONS

• Separate cores into different blocks
• Don’t ink cores
  • A dab of hematoxylin before processing works!
• Don’t exhaust the block in ‘gray-zone’ cases (especially those that are ground glass on imaging)
  • 2-3 deeper sections in challenging cases ok
  • Preserve remaining tissue for molecular
• Limited panel (if needed), TTF-1, p40
MICROPAPILLARY PATTERN: EXPANDED

• Classical/Floret
• Filigree
  • Delicate lace-like narrow stacks
  • At least 3 nuclei piled outwards (avoids tangential cut issues)
• No fibrovascular cores
MICROPAPILLARY SPECTRUM

- Stromal pattern
  - Nests of micropapillary cells infiltrating in the stromal

- Airspace MP in acinar/papillary
  - Default should be MP

- Rings

- Single cells

- Psammoma bodies not uncommon (might be clue that MP is overlooked)
Sneaky micropapillary filigree pattern
STAS (SPREAD THROUGH AIR SPACES)

- Manifestation of tumor spread (*not* included in tumor size)
- Tumor cells within airspaces in the lung parenchyma beyond the edge of the main tumor
- Predictor of worse clinical outcome, especially in limited resections
STAS - CAVEATS

• Not recommended to report amount/size or distance of STAS from main tumor

• Artifacts
  • ‘Tumor butter’
  • Lifted linear strips of tumor
  • Lack of continuous spread from tumor to edge – clue to an artifact
Lifted linear strips – can mimic STAS
‘Tumor butter’ favored
Deeper levels – connects!

NOT STAS
NEUROENDOCRINE LESIONS

• Neuroendocrine tumors (NET)
  • Carcinoid tumor, NOS – for small bx, metastases or limited sampling
  • Typical Carcinoid/NET, Grade 1 (<2 mitoses per 2 mm$^2$)
  • Atypical Carcinoid/NET, Grade 2 (2-10 mitoses per 2 mm$^2$)

• Neuroendocrine carcinomas
  • Small cell carcinoma
    • Combined small cell carcinoma
  • Large cell neuroendocrine carcinoma
    • Combined large cell neuroendocrine carcinoma
CARCINOID TUMOR, NOS

- Terminology used in 3 settings
  - Distinction between typical and atypical carcinoids
    - Report mitotic count
    - Report presence/absence of necrosis
    - Ki-67 (if available, not required, but is desirable)
  - Metastatic carcinoids
- Situation where only limited slides from a case are available (consults, transfer of care)
KI-97

• Useful in carcinoids versus SCLC or LCNEC (small crushed biopsies)

• Carcinoids and small cell ca and Large NECA are genetically different (not new, but important to recall)
COUNTING MITOSES

• Count in areas of highest mitotic activity and the highest concentration of viable tumor cells (Ki-67 can be useful here in resection cases)

• 2 mm$^2$ (not 10 HPF)

• If near the cutoff, count at least 3 sets of 2 mm$^2$ and the mean used RATHER than the single highest rate

• Only definitive mitoses should be counted
CARCINOID TUMORS WITH ELEVATED MITOTIC COUNTS

- Still not formally recognized in WHO (rare)
- Generally, correspond to the Grade 3 NET of the pancreas (PanNET) – felt to have insufficient data to add to the lung WHO
- 2021: Suggest that these have carcinoid features
NEW GRADING CRITERIA

• Epithelioid mesothelioma
  • Low-grade
  • High-grade
  • Favorable/unfavorable architectural patterns, cytologic features, and stromal features
GRADING OF PLEURAL EPITHELIOID MALIGNANT MESOTHELIOMA

- **Nuclear atypia score**
  - 1 (mild)
  - 2 (moderate)
  - 3 (severe)

- **Mitotic count**
  - 1 (low, \( \leq 1 \) per \( 2\text{mm}^2 \))
  - 2 (intermediate, 2-4 per \( 2\text{mm}^2 \))
  - 3 (high, 5+ per \( 2\text{mm}^2 \))

- **SUM of above**
  - 2 or 3 = nuclear grade I
  - 4 or 5 = nuclear grade II
  - 6 = nuclear grade III

- **Necrosis**: present/absent

- **Low-grade** = Nuclear grade I and II without necrosis

- **High-grade** = Nuclear grade II with necrosis, Nuclear grade II with or without necrosis
HISTOLOGIC CLASSIFICATION

• Unfavorable architectural patterns
  • Solid (≥ 50%)
  • Micropapillary

• Unfavorable cytologic features
  • Rhabdoid
  • Pleomorphic
  • Severe nuclear atypia
HISTOLOGIC CLASSIFICATION

• Favorable architectural patterns
  • Tubulopapillary
  • Trabecular
  • Adenomatoid

• Favorable cytologic features
  • Lymphohistiocytoid
  • Low nuclear grade

• Favorable stroma features
  • Myxoid (≥ 50% of tumor with less than 50% solid pattern contains myxoid stroma)
Nuclear atypia 1
Nuclear atypia 3
Solid pattern
Nuclear atypia
3
Tumor necrosis
Rhabdoid phenotype
NOW, FOR A CASE!
POORLY DIFFERENTIATED CARCINOMA

Initial workup

TTF-1
P40
CK 5/6

NEGATIVE
DDX for tumors with “rhabdoid” cytology

Muscle--Rhabdomyosarcoma
Kidney--Rhabdoid tumor (and other sites!)
Skin--Rhabdoid melanoma
Lung--Sarcomatoid carcinoma
WHAT NEXT?

- Most primary lung tumors are **carcinomas**
- Repeat the markers, maybe in another lab, expand keratin markers
- Do vascular, melanoma, lymphoma markers
- Think about metastases
- Think about tumors with unusual IHC patterns!
  - Thoracic **SMARCA4**-deficient undifferentiated tumor (CK +/-; CD34+, BRG1 lost, INI1 retained)
  - NUT carcinoma (CK focal, TTF1 neg, NUT pos)
THORACIC SMARCA4-DEFICIENT UNDIFFERENTIATED TUMOR

• Undifferentiated high-grade rhabdoid malignancy
• Adults (median age 56, range 19-84), smoking
• Loss of SMARCA4 (BRG1), member of SWI/SNF chromatin remodeling complex
• IHC
  • Variable: keratins, CD34, Sox 10, SALL4, CD34, Synaptophysin
  • Occasionally TTF-1, p63, p40, WT-1 positivity
NOW, FOR ANOTHER CASE!
NOW, WITHOUT EBV POSITIVITY

- Lymphoepithelioma-like carcinoma →
- Lymphoepithelial carcinoma (EBV + and EBV -)
• Bronchiolar adenoma (ciliated muconodular papillary tumor)
• New in the adenoma category
THANK YOU!
QUESTIONS?